PAUL EHRLICH—MAN AND SCIENTIST

ERNST JOKL

University of Kentucky, Lexington, Ky.

May I open this discourse by reading to you a letter received a few days ago from Sir Henry Dale in London:

Dear Dr. Jokl,

"I shall myself be attending, on March 14th and 15th, the celebration which has been organized in Frankfurt to commemorate the centenary of the births of Paul Ehrlich and Emil von Behring. I gladly accept your invitation to send to the Commemorative Meeting at The New York Academy of Medicine an expression of my veneration for the memory of Paul Ehrlich. More than any other man, I think, Ehrlich was responsible for the tremendous revolution in the medicinal treatment of disease which has taken place during the last half century. He had a large share of the responsibility for making immunology a progressive, experimental science. In retrospect, however, his immunological work appears to have been a diversion from, or an opportunist extension of, the main line of his researches. Even from his student days, his mind appears to have been permeated and his activities directed by the idea of a therapeutics based upon specific chemical affinities; and the line of development appears to be direct, from Ehrlich's early work on the use of dyes as micro-chemical reagents, and on the oxygen-needs of the tissues, through salvarsan to the sulphonamides, the antibiotics, and all the great modern wealth of directly curative remedies.

I myself have personal memories of Ehrlich's endearing personality, and I gladly join with you in celebrating the centenary of the birth of this great man of genius, and great benefactor of mankind." Sincerely, — H. H. Dale

Ehrlich was appreciated during his lifetime and indeed received a great deal of recognition, scientific as well as personal. Willstatter, the great chemist, describes in his autobiography how Ehrlich in the last years of his life was persona gratissima with the German Kaiser, and that the strict ceremonial of the Imperial Court did in no way apply to him. However, the working of his mind and the nature of his research were so original that their significance was not immediately understood.

In a letter, Professor Aschheim, the co-discoverer of the pregnancy test, refers to this fact. He writes:

"I attended several lectures Ehrlich gave in Berlin. His discourses were always received with enthusiasm notwithstanding the fact that many among his audience were unable to follow his ideas. It was his custom to ask during his lectures, 'isn't everything perfectly clear?', and everybody shouted, 'Yes, yes'. Who indeed would have admitted to the kind professor that his theories were in fact quite difficult to grasp?"

Today, almost forty years after his death, we are in a better position to draw a picture of the man and the scientist who, as Sir Henry Dale points out, was responsible for the tremendous revolution in the medi-

cinal treatment of diseases which has taken place during the last half century.

Ehrlich's life and his work are characterized by three axiomatic trends of thought. The first of these is that Ehrlich thought in quantitative terms. The second is that he possessed the gift of formulating dynamic, scientific hypotheses which he presented picturesquely as if he were to describe mechanical models. The third is that the leitmotif for Ehrlich's research work was the theory of his teacher, Julius Cohnheim that natural adaptations in pathological processes are unreliable.

As to the first axiom, I quote a paragraph from James Clark Maxwell's "Theory of Heat" to which Ehrlich has frequently referred:

> "The most important step in the progress of every science is the measurement of quantities. Those whose curiosity is satisfied with observing what happens have occasionally done service by directing the attention of others to the phenomena they have seen; but it is to those who endeavor to find out how much there is of anything that we owe all the great advances in our knowledge. Thus every science has some instrument of precision, which may be taken as a material type of that science which it has advanced, by enabling observers to express their results as measured quantities. In astronomy we have the divided circle, in chemistry the balance, in heat the thermometer, while the whole system of civilized life may be fitly symbolized by a foot rule, a set of weights and a clock."

If Ehrlich would have done nothing else than introduced into medical research the principle of measuring, he would have left his mark. This point is well illustrated in the citation of his Nobel Prize in 1908. At that time Ehrlich had not yet started his work on chemotherapy which was to lead to the discovery of salvarsan. Professor Liljestrand of Stockholm, who has reviewed the story of "The Nobel Prize in Physiology and Medicine," writes as follows:

> "Important contributions to the interpretation of the immunity process were made by PAUL EHRLICH (1854-1915). In 1891 he succeeded, for instance, in making test animals immune to certain vegetable poisons (abrin and ricin) and defined the degree of immunity as the ratio between the largest amount of poison an immunized animal can stand and the dose that would kill an untreated one. To develop fully the power of resistance to a poison, a latent period is required, as shown by the fact that the resistance power of the test animals suddenly becomes increased on the sixth day after injection, the degree of resistance depending on the amount of poison injected. When the doses were gradually augmented, a correspondingly greater quantity of antitoxin was produced until there was toleration of several hundred times the amount of poison that would originally have been fatal. While the active immunity thus obtained was not hereditary, it could be transmitted to the offspring by the mother's milk. The application of these results to the production of effective sera has been of outstanding practical value. The same is true of the method devised by Ehrlich to determine biologically the strength of a diphtheria serum. In this test the basic immunity unit is taken to be the amount which in a guinea-pig weighing 250 grammes is able to neutralize one hundred times the amount that would ordinarily cause death.

"The introduction of quantitative methods in immunology caused Ehrlich to attempt an explanation of the immunization process. His conclusions were embodied in his celebrated 'side-chain' theory. Since the antitoxin has a much larger molecule than the toxin, it cannot be a derivative of it, he argued, but must be produced by the living organism's reaction to it. The toxin he supposed to contain special so-called haptophorous groups by which it can be bound to certain cell elements which Ehrlich called receptors, corresponding to the 'side-chains' attached to a benzene ring. These elements are consequently neutralized and made useless for their ordinary metabolic purposes. In the toxin there are, furthermore, so-called toxophorous groups, and with their aid the absorbed agent can attack the cell directly. If the cell survives the attack, new receptors are formed, and, as often happens under extreme strain, the reaction creates a surplus of them; some of the superfluous receptors are then discharged into the blood and the tissue fluid in which they are able to absorb and neutralize the toxin. In certain cases (bacteriolysis, haemolysis) this does not happen until after the immune bodies have become fused with still another element (complement). Just as iron rods, when placed outside a house, can protect it against lightning, while the same rods set up inside it can have the opposite effect, so the receptors, once they have been ejected from the cell, can have a protective influence, whereas inside it they would have increased the effect of the toxins. Between the toxin and the antitoxin Ehrlich assumed that there was a relatively stable chemical relationship.

"A certain amount of criticism has been directed at some aspects of Ehrlich's 'side-chain' theory, especially by S. Arrhenius and T. Madsen, particularly in reference to the relationship between the toxins and the antitoxins, but as a working hypothesis it has undoubtedly had a considerable value. Within the Nobel Committee too, doubts were expressed but a majority was of the opinion that Ehrlich's contributions to immunity research were so outstanding that they deserved a prize. As a matter of fact, since the year 1901, Ehrlich had been nominated about seventy times from thirteen different countries. While by some of his sponsors such achievements as his creation of modern clinical haematology and the discovery that the tubercle bacillus is acid-fast had been cited as arguments for an award, a majority of the nominations were based on his works on immunology. The attitude of the Committee regarding the latter was identical with that of one of his supporters (C. J. Salomonsen) who wrote: 'Whatever one may think of his side-chain theory, there can be no doubt that, since the death of Pasteur, Ehrlich has been the foremost worker in the entire domain of immunology.' Being in accord with that opinion, the Institute awarded one-half of the prize for 1908 to EHRLICH 'in recognition of his works on immunity.'"

During the years between the award of the Nobel Prize in 1908 and his death in 1915, Ehrlich reaped the fruits of his insistence upon measurement in medical research. The classical experiments in which he tried to increase the efficacy of chemotherapeutic substances of known pharmacological trends while at the same time endeavoring to eliminate their toxic side effects were altogether based on this principle. On p. 589 of the Festschrift published on the occasion of Ehrlich's 60th birthday, Hata and Shiga presented a diagram showing exactly the toxicity ranges of salvarsan as against neo-salvarsan. This diagram represented a model for the conduct and presentation of experiments in chemotherapy and pharmacology. In conformity with Maxwell's criteria of scientific procedure, Ehrlich had succeeded in creating a technique of

precision "which may be taken as a material type of that science which it had advanced, by enabling observers to express their results as measured quantities."

As to the second axiom, viz., that of formulating scientific hypotheses as if they were mechanical models, Professor A. V. Hill of London recently said that: "facts alone are apt to be dull things and need to be tied together by theories or applied to practical problems if they are to be made reasonably palatable." And during the last quarter of the 19th century, Lord Kelvin taught in Glasgow that "you cannot have clarity on a scientific concept before you have presented it in form of a model."

The significance of Ehrlich's models must be judged not only from the heuristic value they had for himself and his pupils, but equally so from the fact that until today they have not lost vividness and dynamic quality. I refer to the theories of the "side-chains," of the antigen-antibody-complement pattern, of the "lock and key" symbolism with which he explained the toxin-antitoxin interaction, and of course to the magic bullet, the "zauberkugel" with which he "shot" at pathogenic microorganisms, so as to bring about the therapia sterilisans magna.

As an example of Ehrlich's picturesque presentation of scientific ideas, I quote from his first major work "Das Sauerstoffbedürfnis des Organismus".

> "Exactly how the dye gets into the cell I am not yet sure, but there can be no doubt that its entry into the cell is dependent on the size of the molecule. I imagine it must be so. Just as meteors penetrate into the gaseous atmosphere of the earth, so molecules of the smallest size are projected into the plasma of the cell and remain there, useful in some way or another (as oxygen-carriers for instance), and then are again eliminated."

On another occasion he wrote:

> "I can picture the chemical formulae in my mental vision and I believe that this fact has been of the greatest value to me in my studies. I had foreseen many things in pure chemistry which came to be known much later."

At the time of the award of the Nobel Prize in 1908, Ehrlich's work on chemotherapy had not been started. I shall read to you another passage from Professor Liljestrand's book in which the little known fact is revealed that, if Ehrlich would have been spared a few more years, he would in all likelihood have been awarded a second Nobel Prize in recognition of his discovery of salvarsan.

> "The pioneer in chemotherapeutic research was Ehrlich. When he made his famous investigations of organic arsenic compounds, he could base them, among other things, on P. Uhlenhuth's observation that atoxyl was both a preventive and a remedy for experimental trypanosome and spirilla diseases, and that it also had

a beneficial effect on syphilis in human beings, even if its high toxicity made its use impracticable. Ehrlich then analyzed the composition of atoxyl and subsequently produced a large number of different arsenic preparations which he tested on animals suffering from experimental syphilis. These extensive and laborious investigations, which were made in cooperation with S. Hata, led as is well known, to the introduction of salvarsan (arsphenamine) and neo-salvarsan (neoarsphenamine) as a specific against syphilis and a number of other infectious diseases caused by trypanosomes or by spirochaetes. The results were highly sensational. Although Ehrlich had already received a Nobel Prize in 1908, *he was again nominated* in 1912 and 1913. That his new achievements were not, however, submitted to a special investigation was only natural, since practical experience was still too limited to determine the value of the remedy in the treatment of syphilis, which, of course, was the most important consideration. Because of Ehrlich's death in 1915, the subject was not taken up again; it is now generally admitted, however, that this contribution must be regarded as a landmark in the development of chemotherapy."

The third axiom of which I have spoken, matured early in Ehrlich's career, while he was still a student in Breslau. At that time he was profoundly impressed with the teachings of Cohnheim to the effect that natural adaptations in pathological processes are unreliable.

Before elaborating this point, I must refer to the richness of scientific life in Breslau in the 70's and 80's of the last century. Three great men of this period in particular left their mark upon Ehrlich's mind. The first was Ferdinand Cohn, next to Linnaeus the greatest botanist of all times; a brilliant and kind man, the first biologist to understand the categorical significance of the then newly discovered world of microorganisms; the last encyclopedist of his scientific discipline which since has grown so much that no individual can ever hope to master it in its entirety; and of course, I must mention that Ferdinand Cohn was the discoverer and sponsor of Robert Koch. The second great man of the Breslau period of Ehrlich was Rudolf Heidenhain, successor to the Chair of Physiology of Purkinje, teacher of Pavlov, who worked under him and who wrote in Breslau under Heidenhain's guidance, his first scientific paper. Thirdly there was Julius Cohnheim whom the late Simon Flexner has rightly described as the greatest pathologist of all times. Since his esteemed cousin, Carl Weigert, was Cohnheim's assistant, Ehrlich was very close to Cohnheim's ideas.

Ehrlich was privileged to be taught by these three men. From Ferdinand Cohn he learned how to formulate lively scientific hypotheses and to think in terms of models; from Heidenheim he learned how to measure quantities in biology; and Cohnheim convinced him that in its adaptive reactions to pathological impacts nature is unreliable. As to this point it is indeed fortunate that we have at our disposal the account

which William Henry Welch gave of the teachings of Cohnheim whose assistant he was in Breslau. In 1939 Henry Sigerist made us indebted to him by publishing a new edition of William Henry Welch's address before the 1897 Annual Congress of American Physicians and Surgeons in Philadelphia, entitled "Adaptation in Pathological Processes." In this address Welch, who had then returned from Breslau to this country, explained how

> "Cohnheim did not regard pathology as a static, recording science, as most of his contemporaries did. He sought comprehensive theories to interpret the ever-increasing volume of unconnected facts as experimental and anatomical research revealed them. 'Adaptation in pathological processes' he said, 'cannot be looked upon as bringing about rational adjustments to the changed conditions created by a causative pathological event.' He stressed his belief that one fails to see in pathological adaptations 'that co-ordinate and special fitness which we are accustomed to find in physiological adaptations.'
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> "In order to illustrate his arguments, he first subjected to an analysis the pathological process of compensatory hypertrophy of heart muscle. He arrived at the same result as had been reached before him by Nothnagel, namely, that 'no teleological idea or form of language need enter into the explanation of the mechanism of the process.' Pathological reactions, he maintained, may or may not be of 'therapeutic' significance. Frequently they even greatly aggravate the seriousness of the case, as he exemplified in the case of certain clinical aspects of inflammation: — —
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> "The more severe and extensive the inflammatory affection, the more serious, as a rule, is the condition of the patient. The surgeon sees his wounds do well or ill according to the character and extent of inflammatory complications. Measures directed to the removal of inflammatory exudation, such as the evacuation of pus from an abscess or an empyema, are the most successful methods of treatment, and the rules are embodied in ancient surgical maxims. How can one conceive of any purpose useful to the patient served by filling the air-cells of his lung with pus-cells, fibrin and red corpuscles in pneumonia, or bathing the brain and spinal cord in serum and pus in meningitis? The closure of pathological defects by new growths of tissue is a process which must be regarded as adaptive. But one would hardly describe as advantageous the scar in the brain which causes epilepsy. If nature has no better weapons than those to fight pneumococcus or meningococcus, it may be asked, what is their use but to drive the devil out with Beelzebub?"

Up to the time of his Nobel Prize, Ehrlich had hoped to develop the revolutionary method of treatment, the therapia sterilisans magna of which he had dreamed since his youth, by adjusting, manipulating, and improving the very weapons which nature itself uses. When von Behring discovered the diphtheria antitoxin, it was Ehrlich who realized that in concentrations in which nature produces this substance, its therapeutic potency would be limited. He therefore set about to make antitoxin available in very much higher titers. There is scarcely a normal immunological phenomenon whose therapeutic potentiality Ehrlich had not tried to utilize; but it was only during the last years of his life when he relied altogether on non-natural, non-physiological substances,

on aniline dyes, on metals and on chemicals of all sorts, that he succeeded in producing his "magic bullets." The direct line of development from "Ehrlich's early work on the use of dyes as micro-chemical reagents," of which Sir Henry Dale writes in his letter, "and on the oxygen needs of tissues, through salvarsan to the sulphonamides, the antibiotics, and the great modern wealth of directly curative remedies;" this line represents the ultimate application of Cohnheim's thoughts. Of course, Cohnheim himself had been influenced by Virchow, and Virchow by Rokitansky. Still, the laurel belongs to Ehrlich.

I like to refer to an analogous situation in the world of music to which Sigmund Spaeth has drawn attention, a situation in which a master chose to devote his genius to the perfection of an idea which had matured before his time.

> In the St. Matthew Passion, written for a Good Friday service in Leipzig, Johann Sebastian Bach made striking use of the chorale, O Haupt voll Blut und Wunden (O Sacred Head now wounded), which occurs five times in the course of the work. This seems to have been his favorite of all the Lutheran hymn tunes that came out of the old German folk-music, for he used it again in his Christmas Oratorio, with the words Wie soll ich dich empfangen? (How shall I then receive Thee?), a regular Advent hymn, to which he evidently wished to give a touch of Lenten prophecy. It also appears in four of Bach's cantatas and in his Choralgesange.
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> This wonderful melody fully deserved such attention. It was known first in 1601, as a secular love-song by Hans Leo Hassler, Mein G'mut ist mir verwirret von einer Jungfrau zart (My spirit is distracted all through a maiden fair). Neither Martin Luther nor Johann Sebastian Bach was inclined to overlook good music merely because its sentiments might not be entirely religious. In 1613 Christoph Knoll had already made a hymn of the lovesong, beginning "Herzlich thut mich verlangen nach einem sel'gen End." ("My longing is most hearty toward a blessed end.") In 1620 a poet named Schneegass changed the words to "Ach Herr, wir armen Sunder" ("O Lord, all we poor sinners"), and in 1656, still nearly thirty years before Bach's birth, Paul Gerhardt established the song as a Lenten chorale, with the words that now appear in the Lutheran hymn-books and in the St. Matthew Passion.

Ehrlich was an impressive personality notwithstanding the fact that he was modest and certainly did not set out to impress. A great number of his contemporaries have dealt at length with their reminiscences of him. I have quoted to you Sir Henry Dale and Professor Aschheim. I have received a delightful appreciation of Ehrlich from his distinguished publisher, Dr. Ferdinand Springer in Heidelberg who earned Ehrlich's special gratitude by sponsoring the fine biography of his cousin Carl Weigert whose scientific excellence was, to Ehrlich's sorrow, not reflected in his academic advancement. Dr. Springer also placed the resources of his publishing house at Ehrlich's disposal when together with Dr. Hata the manuscript of his book "Die experimentelle

Chemotherapie der Spirillosen" was completed, and he published the biography of Ehrlich by his former secretary, Miss Marquardt.

Dr. Chaim Weizman in his book "Trial and Error" writes at length of a meeting with Ehrlich. Friedrich von Müller, the celebrated Munich internist, devotes a warm personal reference to him.

Many valuable links exist between Ehrlich and this country. Landsteiner and Michaelis, his master pupils, worked for many years in New York. Ehrlich's daughters and his gifted grandchildren, Dr. Hans Wolfgang Schwerin and Mr. Gunther Schwerin actually live in New York. I have enjoyed the friendship of the Schwerin family since my childhood and I remember with pride, that I met Ehrlich shortly before his death in their hospitable home in Breslau. Ehrlich's cousin, and devoted co-worker, the great dermatologist, Professor Felix Pinkus, came to this country in 1940. He died in Detroit where his son Herman continues in the footsteps of his father. The nephew of Professor Edinger, the neurologist, one of Ehrlich's closest friends of his Frankfurt period actually is today with us. I refer to the Consul General of the West German Republic, Dr. Hans Riesser, whose brother Otto was a pupil of Ehrlich.

When Ehrlich died in 1915 Professor Arnold Berliner wrote a memorable obituary in the "Naturwissenschaften" of September 3rd, which concluded as follows:

> "At dawn of history," so Goethe tells us, "men held a solemn and sometimes terrifying belief. They imagined their ancestors seated in silent communion in great caves in a circle of thrones. When a new soul entered this company, they would stand and bow to welcome him if he was worthy enough. The ancestors are the great men whose services to humanity are recorded in the Book of Eternity. We can be sure that they will bow deeply in profound veneration to the man now entering their presence."

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